Sexually transmitted hepatitis: a review

R J C Gilson

Introduction

Viral infections principally affecting the liver, are among the sexually transmitted diseases with the highest incidence worldwide. The most important of these is infection with hepatitis B virus (HBV), which is estimated to be responsible for chronic infection in at least 300 million individuals and is the ninth major cause of premature mortality. Hepatitis A virus (HAV) is rarely acquired sexually. Hepatitis E (HEV) has recently been characterised and is transmitted by the faecal-oral route, like HAV.[1] Outbreaks of HEV infection have been described particularly in Asia. There is a high mortality among pregnant women (10%) for which there is so far no explanation. There is no evidence yet of sexual transmission of HEV; however the possibility of oro-anal transmission among homosexual men, as has been documented for HAV infection cannot be discounted. It will not be considered further here. Hepatitis D virus (HDV) affects only those simultaneously or already, chronically, infected with HBV. Sexual transmission does occur, but in developed countries most infections are associated with injecting drug use.

Hepatitis C virus (HCV) is another agent which has been recently characterised and is the major cause of parenterally transmitted non-A, non-B hepatitis (NANBH).[2] Although the physico-chemical properties of the virus had been predicted correctly, for some years it eluded further characterisation owing to the low titre of virus in serum. Using serum known to have transmitted NANBH, Choo *et al* eventually cloned a sequence from a non-structural gene (NS4).[3] The product of this gene reacted with other NANBH sera, and was used to make the first diagnostic assay for antibodies to HCV.[4] HCV is a small RNA virus (9.1 kilobases) most closely related to the flaviviruses (eg dengue fever virus) and pestiviruses.[5] By analogy with these viruses, there are nucleocapsid and envelope proteins coded for at the 5' end, and four non-structural gene products. Initial studies employing the first generation anti-HCV assay were complicated by the lack of a confirmatory assay. False positive reactions were suspected with sera from patients with chronic liver disease[6] and from tropical communities.[7] Second generation assays include a structural (nucleocapsid) gene-product. About 80% of cases of post-transfusion hepatitis are now attributable to HCV,[8] although other antibody-antigen systems may be identified which will reveal additional cases. Delayed seroconversion after acute infection is common. Compared with the first-generation, second-generation anti-HCV assays are more likely to detect infection within 6 weeks (60% versus 45%; MJ Alter personal communication). No serological assays have yet been developed for HCV antigens. Assays for viral RNA in serum have been developed. These employ a reverse transcription step followed by polymerase chain reaction (PCR) amplification of cDNA.[9-11]

Academic Department of Genito-Urinary Medicine, University College and Middlesex School of Medicine, The Middlesex Hospital, London WIN 8AA, UK
R J C Gilson

Epidemiology of sexually transmitted hepatitis

Hepatitis B

The strongest epidemiological association between sexual behaviour and hepatitis B virus infection is among homosexual men. First suggested in 1970,[12] there followed a series of studies of the prevalence of HBV infection among homosexual men attending genitourinary medicine (GUM) clinics in Europe and North America. Previous or current infection was found in 50–75% with an HBV carrier rate of 1·5–4% (table).[13-25] The major risk factor for transmission is unprotected anal intercourse.[14] The biological plausibility of this mode of transmission was supported by the demonstration of hepatitis B surface antigen and HBV-DNA in semen; HBsAg has also been detected in swabs from superficial asymptomatic rectal mucosal lesions.[26]

In the United Kingdom there was a rise in the total number of reports of acute HBV infection to the Communicable Disease Surveillance Centre (CDSC) to a peak of 1995 reports in 1984.[27] Although the number of reports has declined since, the proportion associated with male homosexuality remains at approximately 7·5% of the total. Since 1988, there has been some evidence that the numbers are increasing again. The decline in reports in the 1980s cannot be explained by the use of vaccine, and is probably related to changes in behaviour. A similar change has been observed in the United States.[28]

Evidence for the role of heterosexual intercourse in the transmission of HBV infection was obtained from an early prevalence study at a genitourinary medicine (GUM) clinic in which a raised prevalence of HBV markers, compared with the general population, was found and HBV marker prevalence was associated with a higher number of sexual partners.[13] More recent studies among heterosexuals attending GUM clinics have shown wide geographical variation (table), reflecting the difference in the general population prevalence in those areas. A case control study in the United States suggested that 23% of cases of acute HBV infection may be attributable to heterosexual transmission.[29] There has been no similar study conducted in the United

Table Studies of the prevalence of hepatitis B virus serological markers in patients attending genito-urinary medicine clinics

City and year of study or publication	Sample size	Serological marker	Homosexual Male	Heterosexual Male	Heterosexual Both	Heterosexual Female	Reference
			% seropositive				
London 1973	974	HBsAg/anti-HBs	19·3		4·2		13 (Fulford *et al*)
New York 1975	597	HBsAg		1·4		1·2	14 (Szmuness *et al*)
		HBsAg/anti-HBs		20·4		11·5	
London 1977	600	HBsAg	5·2				15 (Coleman *et al*)
London 1979	2612	HBsAg	4·9				16 (Ellis *et al*)
Copenhagen 1980	280	HBsAg	10·5	0		0	17 (Hentzer *et al*)
		Anti-HBs	28·4	12·8		8·8	
5 US Cities 1982	3816	HBsAg	6·1				18 (Schreeder *et al*)
		Anti-HBc/anti-HBs	61·5				
Sydney 1984	612	HBsAg	3·3	1·5		0·5	19 (Christopher *et al*)
		Anti-HBc	64·3	13·9		13·5	
Leeds 1981–4	522	HBsAg/Anti-HBs	31·0				20 (Kinghorn *et al*)
Sheffield 1984–5	293	HBsAg/Anti-HBs	16·0				
London 1982	153	Anti-HBc	40·5				21 (Carne *et al*)
1984	153	Anti-HBc	50·3				
West Berlin 1986	666	HBsAg	6·6				22 (Hess *et al*)
		Anti-HBc	60·8				
Phoenix 1986	379	Anti-HBc/anti-HBs			9·0		23 (Alter *et al*)
London 1987	1061	Anti-HBc	48·0	7·5		10·8	24 (Gilson *et al*)
Rome 1988	1116	HBsAg	6·5		5·3		25 (Mele *et al*)
		Anti-HBc	68·8		41·8		
London 1990	1583*	Anti-HBc	49·0	6·0		3·6	Gilson (unpublished)

**excludes injecting drug users and hepatitis B vaccinees*

Kingdom. The current system of reporting of HBV infections to CDSC does not permit an accurate estimate of the proportion acquired heterosexually. Although 7% are attributed in this way, an increasing proportion of cases are not associated with an identifiable risk factor (approximately 40%).[27] As in the United States, it is suggested that many of these cases may also be attributable to heterosexual contact and could further increase the relative importance of this mode of transmission.

In countries with a very low prevalence of HBV infection in the general population, such as the United Kingdom, individuals from other higher endemicity countries and those with a history of injecting drug use may contribute substantially to the prevalence. Injecting drug users are at risk both from the sharing of injecting equipment and by sexual transmission from other drug users; their non-drug-using partners are also at risk.

Hepatitis A

Hepatitis A virus is spread by the faecal-oral route and sexual transmission is thought not to be a major mode of transmission although there is evidence for an increased risk among homosexual men. An excess of cases of non-B hepatitis in men age 20-40 years was reported in San Francisco in 1979, before the development of specific HAV assays.[30] A study of attenders at a GUM clinic in Seattle, USA[31] found a prevalence of anti-HAV of 30% among homosexual men with multiple sexual partners compared with 12% among heterosexual controls drawn from a study of recurrent genital herpes. They also demonstrated an increased attack rate (22% per annum) during a 6-9 month follow-up period with no infections among heterosexual controls. Evidence for transmission of HAV among homosexual men has been reported from London,[32] and an epidemic documented in Scandinavia.[33] Recently, an increasing number of cases of hepatitis A among homosexual men have been reported.[34] Although the incidence in the general population is at a peak in a 10-year cycle this is not enough to explain the number of reports among homosexual men. The increase may be related to the increased prevalence of oroanal intercourse being adopted as a "safer" practice with respect to HIV transmission, but which still permits transmission of HAV.[35]

Hepatitis D (Delta)

The group most affected by HDV is injecting drug users particularly in Europe and North America where it is an important additional cause of acute and chronic hepatitis.[36 37] Studies in Europe and the USA[38 39] have found surprisingly little HDV infection among homosexual men. One more recent study from France found a prevalence of 14% among 42 homosexual male hepatitis B carriers without a history of injecting drug use[40] but the prevalence in a similar population in London remains very low (Waite J, personal communication).

Hepatitis C

In an epidemiological study Alter *et al* showed that sexual contact was a risk factor for acute non-A, non-B hepatitis.[29] Further evidence for the sexual transmission of HCV was provided by early observations of a raised prevalence in homosexual men[41 42] on a background of a low prevalence in the general population.[10] A retrospective longitudinal study among 259 homosexual men in Denmark followed between 1981 and 1989 found that seroconversion for anti-HCV was rare with a cumulative incidence of 4·1% and suggested that the acquisition or presence of this antibody was unrelated to sexual lifestyle.[43] In contrast, a cross-sectional study at a London GUM clinic, found a higher prevalence among homosexual men than heterosexual men and women.[44] In this study, anonymised syphilis serology samples analysed for HIV-seroprevalence[45] were screened using a first generation anti-HCV assay (anti-C100, Ortho Diagnos-

tics) with confirmation of specificity using a recombinant immunoblot assay. The prevalence was 2·2% among homosexual men and 0·4% among heterosexuals

Injecting drug users have a much higher prevalence of HCV infection, typically 50–70%.[2] In another GUM clinic study in which only 1% of the population had a history of injecting drug use, or contact with a user, half of the HCV infections were associated with drug use (Gilson, manuscript in preparation). This is consistent with the proposition that HCV infection is much more efficiently transmitted by needle sharing than by sexual intercourse. Studies of sexual partners of known anti-HCV-positive patients have found a low prevalence among partners, together with some evidence of infection in other household members, making it difficult to identify the routes of transmission.[46]

Other hepatitis viruses

Evidence for sexual transmission exists for cytomegalovirus (CMV). Studies of homosexual men have found a high prevalence of antibodies to CMV (90–95%) compared with age-matched heterosexual controls (50–60%).[47,48] CMV, however, is a rare cause of acute hepatitis, most infections being asymptomatic. In patients with HIV infection who are immunosuppressed, a variety of hepatic disorders are recognised including adverse effects of drugs, reactivation of CMV, atypical mycobacterial infection and liver disease secondary to sclerosing cholangitis.[49–53] There is no evidence of a primary hepatic disorder related to HIV infection. These other causes of hepatitis will not be considered further in this review.

Clinical features and natural history

Hepatitis B

Only about 25% of cases of HBV infection give rise to the typical symptoms.[54] Most patients recover without becoming carriers, and develop protective levels of anti-HBs. Antibody to HBV core (anti-HBc) does not distinguish between current and previous infection, appearing early and persisting in almost all patients. Anti-HBc-IgM is detectable during acute infection but may also be detectable persistently at low titre in the 5–10% of patients in whom serum HBsAg is still detectable after six months and who have become, by definition, chronic carriers. Factors associated with higher rates of carriage include asymptomatic rather than symptomatic acute infection,[55] age of acquisition (up to 90% among neonates and declining to adult rates by age 8–10 years)[56] and prior HIV infection. Among homosexual men in one study, the carrier rate was increased from 6% in HIV-negative to 20% in HIV-positive patients,[57] although HIV-positive patients may be more likely to have a symptomatic acute infection.[58]

Serum HBV e-antigen (HBeAg) appears early in acute infection and persists in carriers. Initially, there are high levels of serum HBV-DNA and HBV-DNA polymerase activity[59] but liver enzymes are near normal. Although histologically the liver may be normal, HBV core antigen is detectable in liver cells. With time, an increased immunological response to infected hepatocytes results in an increase in liver transaminases and the development of chronic active hepatitis histologically. This may be associated with a fall in serum HBV-DNA and eventually seroconversion from HBeAg to anti-HBe positivity. The trigger for this process is uncertain. Exceptionally, some patients have anti-HBe detectable in serum but high levels of serum HBV-DNA and severe liver disease. This has been associated with a point mutation in the pre-core gene producing a stop codon and preventing translation of the gene coding for HBeAg.[60] Mixture of wild-type and mutant viruses have been reported and it is not clear yet whether the presence of the mutation is causally related to the severe liver disease and anti-HBe seroconversion or simply a marker for the presence of anti-HBe.

Loss of serum HBeAg in carriers, associated with a reduction in infectivity, occurs spontaneously at approximately 10% per year.[61] The cumulative risk of developing progressive chronic liver disease is estimated at about 20%. There are a number of interactions between chronic HBV and HIV infections. Patients who also have HIV infection have a significantly lower rate of spontaneous loss of serum HBV-DNA[62] or HBeAg (approximately 5% per annum),[63] have higher levels of viral replication[64] but less severe liver disease, either biochemically[62,65] or histologically.[64,66,67] It is not known whether HIV infection affects the rate of development of end-stage liver disease.

Hepatitis D

Hepatitis D virus is a defective RNA virus which requires concurrent infection with HBV to permit productive viral replication.[68] Simultaneous infection causes a combined acute hepatitis which typically resolves without sequelae. Super-infection of an individual with chronic HBV infection may precipitate rapid progression of chronic hepatitis.[69]

Hepatitis A

The proportion of cases of hepatitis A with symptoms increases with age. It is estimated that 90–95% of cases in children up to age 5 years are asymptomatic, but over 90% of cases in adults are symptomatic.[70] In many industrialised countries improvements in hygiene have resulted in fewer cases in childhood so that an increasing proportion of the adult population are still susceptible. Overall the proportion of symptomatic cases is therefore increasing. There is no carrier state following hepatitis A virus infection.

Hepatitis C

Like the other acute hepatitis virus infections most acute cases of hepatitis C are asymptomatic and resolve spontaneously; however, the carrier rate is higher than that for hepatitis B, estimated at 30–50%.[2] Also unlike HBV, hepatitis C virus may be directly cytopathic in

the liver. Patients with HCV infection may develop progressive chronic liver disease and cirrhosis. There is an increased risk of hepatocellular carcinoma, although it is uncertain whether this is a direct carcinogenic effect of HCV as has been proposed for HBV, or whether it is secondary to the development of cirrhosis.[71]

Treatment

Treatment of acute viral hepatitis is conservative. Most patients do not require hospital admission but liver function tests and the prothrombin time should be monitored. Fulminant hepatic failure although very rare was almost universally fatal, but, improvements in treatment including liver transplantation now offer more hope.[72]

The aim of treatment of chronic HBV infection is to reduce the risk of developing end-stage liver disease. Recently alpha interferon has been licensed for the treatment of chronic hepatitis B in the United Kingdom after clinical trials extending over more than 10 years. The treatment still remains controversial however, partly because the response rate in terms of seroconversion from HBeAg to anti-HBe is only of the order of 30–50%, and partly because side-effects are common and treatment is expensive.[73] Loss of serum HBsAg occurs in only 5% of cases; too infrequent to be a goal of treatment. Careful selection of patients to increase the probability of a response, for example those with low HBV-DNA and raised transaminase, also identifies those with an increased probability of spontaneous seroconversion, which may be preceded by a transient rise in transaminases. One approach may be to reserve treatment for those patients with persistently raised transaminases (for example three times the upper limit of normal) who have not seroconverted spontaneously after six months.[74] Homosexual men and those with HIV infection are less likely to respond to treatment .[75 76] The urgent need is to find ways to increase the response rate probably by combining interferon with another agent, either an immunostimulant or an antiviral agent. There are no immediate prospects in this respect. Adenine arabinoside monophosphate was probably the most promising however its use is limited by toxicity.[77] The search for antiviral compounds for HIV infection may lead to further agents being found with activity against HBV. Steroid treatment prior to interferon therapy, with the aim of enhancing HBcAg display and hence immune clearance of infected hepatocytes has been disappointing. Most patients receiving interferon are treated for 3–4 months with a usual dose of 5–10 MU given subcutaneously three times a week. Although an induction period of daily treatment for a week was often included in trials, there is no evidence that this is necessary.

Treatment of hepatitis A is conservative with complete resolution in almost all cases. Relapse shortly after acute infection and persistent cholestasis have been described but resolve. Fulminant hepatic failure is very rare.

Treatment of chronic hepatitis C is still being evaluated, although alpha-interferon has been licensed for this indication in some countries. Approximately 50% of patients may respond to interferon with normalisation of transaminase levels; however, half of these will relapse when treatment stops.[78 79] There are insufficient data to recommend any particular dose or duration of treatment but most trials have used lower doses than for hepatitis B (1–3 MU three times per week) and for longer (6–12 months). Recently a reduction in HCV viraemia during interferon treatment has been demonstrated using semi-quantitative PCR, providing further direct evidence of its antiviral effect, and establishing a method to evaluate other agents.[80]

Prevention

Hepatitis viruses differ in their mode of transmission and their infectivity. Hepatitis B is the first against which a vaccine has been developed, and indeed the first sexually transmitted disease against which we have an effective vaccine.[81] Transmission of HBV can be reduced by adopting safer sexual practices as widely promoted for the prevention of HIV infection. HBe-antigenaemic patients are more infectious that those who have lost HBeAg, with or without the development of anti-HBe. Overall, HBV infection is more infectious than HIV with higher rates of infection among regular partners. There is also evidence of household transmission of HBV in contrast to HIV.

Specific protection is provided by active immunisation using an HBV surface antigen vaccine. More rapid protection can be provided by hepatitis B hyperimmune globulin but it needs to be given within 48 hours of exposure, is of limited availability and is expensive. Its use is largely restricted to situations where the exposure is recent and well defined such as occupational incidents among health care workers, and babies born to carrier mothers, when it is given in combination with vaccine.

Synthetic HBsAg vaccines are produced by recombinant DNA technology in yeast cells and have largely replaced the equally safe and effective plasma-derived vaccines which were less easy and more expensive to produce in large quantities. The course of three doses of vaccine should be given intramuscularly into the deltoid. Intradermal injection of a smaller dose is not recommended because although possibly cheaper, it is technically more demanding, does not usually induce such high antibody titres, and qualitative differences in the immune response mean that equivalent efficacy cannot be assumed.[82] Failure of vaccine programmes using the intradermal route have been reported largely due to problems of poor technique.[83] Following a standard three-dose course, about 95% adults will have a protective level of antibody (> 10 mIU/ml anti-HBs). Because the duration of effect is

related to the peak titre, those patients with a poor response (below 100 mIU/ml) may be given a further single booster dose. The level of protection is high with a 90% reduction in the attack rate of infection in the early clinical trials among homosexual men. Recently, failure of protection has been reported among contacts of HBV carriers in Italy, including infants of carrier mothers.[84] One of these patients, who was given hyperimmune globulin at birth but did not receive vaccine until 3 months, was found to have a virus with a point mutation in the surface gene which altered the *a* determinant against which most of the vaccine-induced humoral response is directed. There is no evidence yet that this is other than a rare event, but awareness of the possibility is important.[85]

Recommendations for the control of HBV infection in general, and sexual transmission in particular[86] must take account of the widely varying prevalences in different countries not only between industrialised and less developed countries but even for example within Europe. In Italy the prevalence of infection is sufficiently high to have lead to a decision to give routine infant and adolescent immunisation. These measures, particularly infant immunisation alone, will take many years to affect the rate of sexual transmission of HBV infection.

In countries highly endemic for HBV infection, for example those in South-East Asia,[86] most infections occur by vertical transmission or by horizontal transmission among young children. These are the main sources of chronic infections and those responsible for the maintenance of infection in the population. Universal immunisation of infants is therefore the primary control strategy. However, the risk of sexual transmission is still high for the 40-60% of the population who have reached adulthood without having been exposed, because of the high prevalence of carriers in the population. This situation will persist until the first cohorts of immunised children reach adulthood. In these circumstances a targeted vaccine policy for sexual contacts, sex industry workers, injecting drug users and homosexual men, in addition to universal infant immunisation may still be appropriate.

In the United States, a policy of selective immunisation of neonates at high risk of HBV infection has now been replaced by a policy of universal infant immunisation. Consideration is now being given to introducing universal adolescent immunisation, which would then be phased out when the first cohort of immunised infants reached adolescence.[87]

In the United Kingdom, a country with a low prevalence of infection, those recommended to receive hepatitis B vaccine include sexual and household contacts of known HBsAg-positive patients, injecting drug users and those who change sexual partner frequently whether homosexual or heterosexual.[88] Although it has been shown to be cost-effective to immunise homosexual men,[89] the reported reduction in incidence of HBV infection since the early 1980s raises doubts about the appropriateness of this policy now. In addition, the reduction in vaccine response rate to approximately 50% in HIV-positive patients[91] will reduce vaccine effectiveness. On the other hand, the higher carrier rate among those with HIV infection who contract HBV infection, and the extended period of highly infectious HBe-antigenaemia will increase the potential benefits of prevention. Similar arguments apply to injecting drug users.

The routine immunisation of all heterosexual patients attending GUM clinics in the United Kingdom remains controversial. In favour of such a policy is the strong evidence for sexual transmission, an effective vaccine and evidence that GUM clinic patients are at increased risk. Against, is the uncertainty regarding the extent to which such a policy would control the sexual transmission of HBV infection in the population and at what cost. We lack important data. The incidence of infection is uncertain, as is the proportion of those at risk who may be reached by a targeted programme. The acceptance rate and likely compliance with the vaccine course is unknown. One further factor which is difficult to quantify is the additional benefit of preventing secondary infections: by immunising one patient, that individual is protected and is prevented from transmitting the infection to subsequent contacts and so on.

There have been no studies of compliance among heterosexuals. In a study of homosexual men attending a GUM clinic, arguably a more motivated group because of their greater exposure to HBV, 30% of patients did not complete the course.[92] The largest failure however was in not offering screening and subsequent immunisation to those at risk.

Universal immunisation in childhood or adolescence may be the most predictably effective way of controlling HBV infection given the reservations above. But a targeted programme could still be effective if it reached a substantial proportion of those adults most at risk, which might equate with GUM clinic attenders. It would have the advantage of taking effect much quicker than any universal strategy.

Protection against hepatitis A can be provided by human normal immunoglobulin injections, but this is less effective and of shorter duration than active immunisation. The first commercially available hepatitis A vaccines are expected to be licensed shortly and studies suggest that they are immunogenic although only limited efficacy data has been collected to date.[93] In the future, combined HBV and HAV vaccines will be available.

There is no specific method of prevention of hepatitis C. There is no evidence that immunoglobulin preparations currently available provide any protection. A vaccine may eventually be developed.

Hepatitis D, because it requires prior or simultaneous HBV infection can be prevented if HBV infection can be prevented. In patients who are already HBV carriers, no specific protection is available. This reinforces the need to discourage continued needle sharing among injecting drug users, which is also central to

HIV prevention measures.

Viral hepatitis remains an important sexually transmitted disease worldwide. Hepatitis B is preventable, although strategies for the use of hepatitis B vaccine need to be appropriate to the epidemiology of infection in particular populations. Prevention of post-transfusion hepatitis C will have largely been achieved, since screening of donations for anti-HCV has been implemented in many countries. The rapidly increasing knowledge of hepatitis C will lead to more information concerning the risks and consequences of sexual transmission.

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